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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,284	08/18/2005	Jorg Mayer	ZIMR/0016	2008

26290 7590 03/05/2009

PATTERSON & SHERIDAN, L.L.P.
3040 POST OAK BOULEVARD
SUITE 1500
HOUSTON, TX 77056

EXAMINER	
SASAN, ARADHANA	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
03/05/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,284	MAYER ET AL.	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 17-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 17-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/25/05 & 09/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks, amendments, and Request for Continued Examination filed on 12/01/08 are acknowledged.

2. Claims 1, 18 and 24 were amended.

3. Claims 1-12 and 17-29 are included in the prosecution.

Continued Examination under 37 CFR 1.114

4. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/01/08 has been entered.

Response to Arguments

Rejection of claims 1-3, 5-11, 17-20, 22-24, 27, and 29 under 35 USC § 103(a)

5. Applicants' arguments, see Page 7, filed 12/01/08, with respect to the rejection of claims 1-3, 5-11, 17-20, 22-24, 27, and 29 under 35 USC § 103(a) as being unpatentable over Parikh et al. (US 2002/0106403) in view of Caruso et al. (EP 1 116 516) have been fully considered but are not found persuasive.

Applicants argue that Parikh does not teach or suggest capsules having a core and a shell structure.

This is not persuasive because Parikh teaches microparticles and phospholipid coated drug particles (Page 2, [0012] and Page 4, [0025]). The core comprises the drug particle and the shell comprises the phospholipid. The structure is taught by Parikh.

Applicants argue that Parikh does not teach, suggest, or otherwise render obvious "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient, the shell comprising a high permeability to release the slightly soluble active ingredient within 60 minutes," as recited in amended claim 1.

This is not persuasive because Parikh teaches rapid disintegration times (less than 2 minutes) (Page 4, [0024]). A rapid dissolution rate of the active ingredient from the microparticles (5-60 sec) is also disclosed (Page 4, [0025]). The shell of the microparticle implicitly allows diffusion and release of the active ingredient because of the rapid disintegration and rapid dissolution times. Parikh also teaches that the rate of dissolution and release can be intermediate (75% disintegration in 15 minutes), thereby implying that the shell of the microparticle allows the diffusion and release of the active ingredient such that 75% of the microparticles disintegrate in 15 minutes, i.e., a stable aqueous suspension during release of the active ingredient is implicit.

Applicants argue that the surface modifier (alleged to be the "shell" by the Examiner) is not equivalent to Applicants' shell because Parikh does not teach that the surface modifier is stable and water-insoluble compound presented within the microparticles can be diffused through the layer of the surface modifier. Applicant argues that Parikh's surface modifier is adsorbed on to the surface of micronized

particles and is dissolved together with the microparticles, which implies a non-stable capsule shell.

This is not persuasive because the surface modifiers disclosed by Parikh include phospholipids, gelatin, and carboxymethylcellulose (Page 2, [0015]). Although Parikh labels these materials as surface modifiers because of their surfactant properties, the fact remains that these form the coating on the core comprising the active material to produce microparticles that have a particle size between 0.05μm to 10 μm (Pages 2-3, [0015] – [0017]). Moreover, Applicants have also disclosed these same materials, particularly a combination of lipids and polymers (including carboxymethylcelluloses) that are used for preparing the capsule shell (Instant Specification, Page 9, lines 9-39).

Applicants argue that Parikh does not disclose that the compound diffuses through a shell but merely dissolves. Applicants disagree with the connection between penetration and dissolution and argue that an object that is dissolvable does not necessarily have to be penetrated, and that penetration requires something sustained in a certain form in order for an object to pass, extend, or diffuse through. Applicants point to Parikh's arguments during the prosecution history of that particular application and argue that it becomes evident that the adsorbed surface modifier, i.e., the alleged shell, is not in a stable status that allows the drug component to diffuse through during release of the drug component, but rather rapidly dissolved together with the drug component in an aqueous environment as described in Parikh's disclosure. Applicants argue that the surface modifier taught by Parikh does not correspond to Applicants' shell which is stable to allow diffusion and release of the active ingredient, while maintaining a stable

aqueous suspension during release of the active ingredient, as recited in amended claim 1.

This is not persuasive because, as noted above, Parikh discloses that materials such as phospholipids, gelatin, and carboxymethylcellulose (Page 2, [0015]) form the coating on the core comprising the active material to produce microparticles that have a particle size between 0.05μm to 10 μm (Pages 2-3, [0015] – [0017]) and that the rate of dissolution and release can be intermediate (75% disintegration in 15 minutes), thereby implying that the shell of the microparticle allows the diffusion and release of the active ingredient such that 75% of the microparticles disintegrate in 15 minutes, i.e., a stable aqueous suspension during release of the active ingredient is implicit. Since the components of the claimed composition (core comprising an active ingredient and capsule shell material) are taught by Parikh along with the particle size and the rapid/intermediate release, one of ordinary skill in the art would find it obvious that the microparticle will be stable for the duration of the intermediate release or dissolution.

Applicants argue that Caruso does not cure the deficiencies of Parikh. Applicants argue that a skilled person, when considering Caruso, would consider Caruso as a sustained release system using a high diffusion barrier across the wall of the capsule for the release of a small amount of active substance and thus would not be motivated to modify Parikh to yield "fast-releasing capsules having a high permeability for the slightly soluble active ingredient," and "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient, and the shell comprising a high permeability to release the slightly

soluble active ingredient within 60 minutes," as recited in amended claim 1. Applicants point to the amended claims 18 and 24 that include the limitation “the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient."

This is not persuasive because microparticles with a shell comprising an amphiphilic phospholipid and alternating layers of polyelectrolytes of opposite charges are known in the art, as evidenced by Caruso (Page 2, [0009] and Page 4, [0019]), which is used as a secondary reference. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the microparticle capsule shell of Parikh by choosing from a finite number of predictable capsule shell materials for microcapsule or microparticle formulations (such as phospholipids and polyelectrolytes with opposing charges), as evidenced by Caruso, with a reasonable expectation of success of producing a functional microparticle that provides rapid disintegration and dissolution of the active ingredient.

Therefore the rejection of 07/29/08 is maintained.

Rejection of claims 4, 25, and 28 under 35 USC § 103(a)

6. Applicants’ arguments, see Page 12, filed 12/01/08, with respect to the rejection of claims 4, 25, and 28 under 35 USC § 103(a) as being unpatentable over Parikh et al. (US 2002/0106403) in view of Caruso et al. (EP 1 116 516) and further in view of Green et al. (US 2001/0055611) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Allen et al. (US 6,187,337 B1).

Rejection of claims 12 and 21 under 35 USC § 103(a)

7. Applicants' arguments, see Page 13, filed 12/01/08, with respect to the rejection of claims 12 and 21 under 35 USC § 103(a) as being unpatentable over Parikh et al. (US 2002/0106403) in view of Caruso et al. (EP 1 116 516) and further in view of Virgalitto et al. (US 2005/0089548) have been fully considered but are not found persuasive.

Applicants argue that although Virgalitto mentions the use of microcapsules containing active agents, Virgalitto's film is rapidly dissolved, break-down and disintegrated upon contact with moisture to release the active agent.

This is not persuasive because microcapsules containing active ingredients, such as pharmaceutical active ingredients, in an edible film (matrix) are known in the art, as evidenced by Virgalitto (Page 1, [0012], and Page 4, [0043]), which is used as a secondary reference. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the matrix composition of Parikh by choosing from a finite number of predictable compositions for microparticles, such as the edible films with microcapsules as evidenced by Caruso, with a reasonable expectation of success of producing a functional film comprising microcapsules that provides rapid disintegration and dissolution of the active ingredient.

Therefore the rejection of 07/29/08 is maintained.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 17, 22, 24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. The term "less than about" is a relative term, which renders the claims indefinite. The term "less than about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Please see MPEP 2173.05(b).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-3, 5-11, 17-20, 22-24, 27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parikh et al. (US 2002/0106403 A1) in view of Caruso et al. (EP 1 116 516 A1).

The claimed invention is a solid dosage form for oral administration comprising a coherent matrix with a disintegration time of less than 2 minutes, wherein: the matrix comprises an active ingredient which is slightly soluble in a physiological fluid and which is in the form of fast-release capsules selected from at least one of micro- and nanocapsules, the capsules comprising a core and a shell, the core comprising the slightly soluble active ingredient, the shell consists essentially of a material with high

permeability for the slightly soluble active ingredient, the shell of the capsules comprising a complex of at least one polyelectrolyte and a counter ion to the polyelectrolyte, the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient, and the shell comprising a high permeability to release the slightly soluble active ingredient within 60 minutes.

Parikh discloses a solid dosage form for oral administration comprising a coherent matrix with a disintegration time of less than 30 seconds (Page 4, [0024]), wherein the matrix comprises an active ingredient which is slightly soluble in a physiological fluid (poorly soluble) (Page 2, [0010]). Parikh discloses mixing the active ingredient with matrix-forming, physiologically acceptable excipients to provide a mixture and forming the mixture into dose units (tablet) (Page 3, [0022]) and the active ingredient is in the form of fast-releasing microcapsules (phospholipid-coated microparticles) (Page 2, [0012] and Page 4, [0025]). Parikh discloses the microcapsules comprising a core (microparticle) and a shell (coating), wherein the core comprises the slightly soluble active ingredient. Since the microcapsule is considered to be rapid-releasing, the shell is also considered to have a high permeability. Parikh further discloses the microcapsules having an average size of less than 10μm (Pages 2-3, [0017]).

Parikh fails to expressly disclose the shell of the microcapsules comprising of at least one polyelectrolyte and a counter ion to the polyelectrolyte.

Caruso discloses using microparticles having shell comprising an amphiphilic (phospholipid) and alternating layers of polyelectrolytes of opposite charges, where the polymer layers are self-assembled by means of electrostatic layer-by-layer deposition (Page 2, [0009], Page 4, [0019]). Caruso further discloses controlling the permeability and porosity of the capsule by controlling the number of layers and by the selection of the polyelectrolytes used for the shell (Page 5, [0032], Page 6, [0036]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition with a matrix comprising fast releasing microcapsules, as suggested by Parikh, modify the composition of the shell of the microcapsule, as taught by Caruso, and produce the instant invention.

One of ordinary skill in the art would find it obvious to modify the matrix composition of Parikh by choosing from a finite number of predictable compositions for microparticles, such as the edible films with microcapsules as evidenced by Caruso, with a reasonable expectation of success of producing a functional film comprising microcapsules that provides rapid disintegration and dissolution of the active ingredient.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding the limitations of instant claims 1, 2, 6-9, 17, 18, 19, 22, 24, 27 and 29, Parikh teaches a solid dosage form for oral administration comprising a coherent

matrix with a disintegration time of less than 30 seconds (Page 4, [0024]), wherein the matrix comprises an active ingredient which is slightly soluble in a physiological fluid (poorly soluble) (Page 2, [0010]).

With respect to claim 3, the modified Parikh discloses the release of active ingredient is virtually complete within 1 minute (Page 4, [0025]).

With respect to claim 5, the modified Parikh discloses the slightly soluble active ingredient is an antihypertensive or a sedative (Page 2, [0013]).

With respect to claim 10, the modified Parikh discloses the matrix is produced by compressing a material selected from at least one of powder and granules (Page 3, [0022]).

With respect to claim 11, the modified Parikh discloses the matrix is produced by freeze-drying a substance selected from at least one of a fluid and a highly viscous composition (Page 2, [0011]).

With respect to claim 20, the modified Parikh discloses mixing the mixture with a liquid carrier (aqueous medium) to provide a solution, wherein forming the mixture into dose units includes dividing and freeze-drying the solution (Page 3, [0018]-[0020]).

With respect to claim 23, the modified Parikh discloses the active ingredient is a therapeutic (Pages 2-3, [0017]).

10. Claims 4, 25-26, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parikh et al. (US 2002/0106403 A1) in view of Caruso et al. (EP 1 116 516 A1) and further in view of Allen et al. (US 6,187,337 B1).

The teachings of Parikh and Caruso are stated above.

Although Parikh discloses gelatin and mannitol as matrix forming agents (Page 3, [0018]), the reference does not expressly teach gelatin and mannitol (in the matrix) in a ratio of 1:1 to 1:3.

Allen teaches rapidly dissolving dosage forms comprising a particulate matrix (Abstract). In examples 32 and 33, the calculated ratio of mannitol: gelatin is 2.9:1 (example 32: 16.0g of mannitol/5.5g total gelatin) and 2.13:1 (example 33: 16.0g mannitol/7.5g total gelatin) (Col. 27, line 30 to Col. 28, line 14).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition with a matrix comprising fast releasing microcapsules, as suggested by Parikh, modify the composition of the shell of the microcapsule, as taught by Caruso, use the ratio of gelatin and mannitol in a rapidly dissolving dosage form, as suggested by Allen, and produce the instant invention.

One of ordinary skill in the art would do this because Allen teaches a rapidly dissolving dosage form and gelatin and mannitol are known components of matrices of rapidly dissolving dosage forms (as evidenced by Parikh and Allen). Where the general conditions of a claim are disclosed in the prior art, discovering the optimum or working ranges involves only routine skill in the art. In re Aller, 105 USPQ 233.

Regarding instant claim 4, the limitation of the matrix further comprising gelatin and mannitol in a ratio of 1:1 to 1:3 would have been obvious over the gelatin and mannitol disclosed by Parikh as matrix forming agents (Page 3, [0018]) in view of the calculated ratio of mannitol: gelatin is 2.9:1 (example 32: 16.0g of mannitol/5.5g total

gelatin) and 2.13:1 (example 33: 16.0g mannitol/7.5g total gelatin) respectively (Col. 27, line 30 to Col. 28, line 14), as taught by Allen. One of ordinary skill in the art would find it obvious to try different levels and ratios of the matrix components during the process of routine experimentation depending on the desired disintegration and dissolution/release rate. The recited ratio of gelatin and mannitol would have been an obvious variant unless there is evidence of criticality or unexpected results.

Regarding instant claim 25, the limitation of the slightly soluble active ingredient would have been obvious over the antihypertensive or sedative taught by Parikh (Page 2, [0013]).

Regarding instant claim 26, the limitation of the average size of the capsule that is less than about 10 μm would have been obvious over the microcapsules having an average size of less than 10μm, as taught by Parikh (Pages 2-3, [0017]).

Regarding instant claim 28, the limitation of the shell of the capsule that comprises a material selected from at least one of a lipid layer and a lipid bilayer would have been obvious over the microcapsules comprising a lipid layer (phospholipid), as taught by Parikh (Page 4, [0025]).

11. Claims 12 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parikh et al. (US 2002/0106403 A1) in view of Caruso et al. (EP 1 116 516 A1) and further in view of Virgalitto et al. (US 2005/0089548 A1).

The teachings of Parikh and Caruso are stated above.

Parikh and Caruso do not expressly teach that the matrix is produced by solidifying a composition which has been spread out into a film.

Virgalitto discloses microcapsules containing active ingredients, such as pharmaceutical active ingredients, in an edible film (matrix) (Page 1, [0012], and Page 4, [0043]). Virgalitto further discloses the matrix is produced by solidifying a composition which has been spread out into a film (Page 5, [0074]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of making the matrix in order to create an alternative oral dosage form for patients that are unable or have a difficult time swallowing conventional oral dosage forms, as taught by Virgalitto (Page 1, [0002]).

Regarding claims 12 and 21, the modified Parikh addresses all the limitations of claim 18, however fails to expressly disclose mixing the mixture with a liquid carrier (inherent to aqueous solution) to provide a solution, wherein forming the mixture into dose units includes spreading the solution into a film and drying the film. Virgalitto discloses the edible film is formed by mixing the mixture (microcapsules and excipients) with a liquid carrier to provide a solution, spreading the solution into a film and drying the film (Page 5, [0074], Page 6, [0076]).

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615